DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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MEMORANDUM

DATE: September 23**,** 1998

FROM: Stephanie L. Simek, Ph.D.
Regulatory Coordinator, Product Reviewer, DARP.

TO: The File

SUBJECT: Review of Container Closure, Drug Substance and Product Stability Data for INF-beta 1a.

TITLE: Original BLA Submission for Rebif (interferon beta-1a) Injection

SPONSOR: Serono Laboratories Inc.
100 Long Water Circle
Norwell MA. 02061

CONTACT PERSON: Thomas Lang
Phone:

Product: Interferon beta-1a

CONTAINER/CLOSURE SYSTEMS The syringes used for the product containment are reviewed by a CDRH consult and are included as a separate review.

Description:

Tubes and Caps:
IFN-beta-1a intermediate and final purified bulk products are stored in XXXXXXXXXX tubes and closed with a plug seal cap (XXXXXXXXXX). The tubes are made of XXXXXXXXXX, and the caps are made of XXXXXXXXXX. Both tubes and caps meet USP class VI requirements for plastic containers and closures. The caps are XXXXXXXXXX and meet CONEG requirements. The tubes are sterilized and shown to be pyrogen free. The container/closure system has been tested and passed an integrity test, centrifugation test, visual attributes and packaging performance testing.

Suitability of Package Components for Intended Use:
The physical, chemical and biological characteristics are reviewed in the MF-XXXXXXXXXX. Specifications, tests, stability, and compatibility issues are also reviewed in the MF XXXXXXXXXX. Resistant ink is used for labeling of pre-filled syringes.

Packaging and Shipment:

XXXXXXXXXX. The containers are stored at XXXXXXXXXX for a maximum of overnight. Once at the airport the cartons are stored at XXXXXXXXXX. Upon arrival at the final formulation site the substance is XXXXXXXXXX. The maximum permitted time for a shipment, from time of packaging until transfer to the XXXXXXXXXX at the finished product formulation site is XXXXXXXXXX.

Shipping Validation:

To verify no alteration occurred during shipping a worst case shipment scenario was tested for bulk batch XXXXXXX XXX. Samples of IFN-beta-1a bulk substance XXXXXXXXXX.

Results:
Table G.4-1 Effect of Worst Shipment conditions on IFN-b-1a
XXXXXXXXXX

Conclusions:
The XXXXXXXXXX results obtained at XXXXXXXXXX did not pass the specification release criteria for worst shipment conditions. All of the other samples passed tests specifications. Based on results from this study, XXXXXXXXXX.
The shipping validation outlined above describes a mechanism to measure any potential discrepancy that might occur during shipping, not a validation of shipping from the site of substance production to finished product formulation site. Shipment of XXXXXXXXXX substance to formulation site, as well as, shipment from formulation site to distribution site needs to be validated to ensure the continual maintenance of appropriate shipping conditions. This will require the use of a thermal measuring devise during shipping.

DRUG SUBSTANCE STABILITY
Batches Tested
Research and Development batches are produced at XXXXXXXXXX and include batch numbers XXXXXXXXXX. Full production batches are produced at XXXXXXXXXX, these include XXXXXXXXXX and qualification batches XXXXXXXXXX which represent product intended for marketing.

General Test Methodology
XXXXXXXXXX

A. Development and Early Production Batches
XXXXXXXXXX

B. Qualification Batches
XXXXXXXXXX

Analytical Test Procedures
XXXXXXXXXX

Conclusion from Analytical Test Procedures
XXXXXXXXXX

Results
XXXXXXXXXX

Table H.6-1 Degradation Rates of IFN-beta-1a bulk stored at various temperatures XXXXXXXXXX

Conclusion

From the data presented above the sponsors are requesting a retest period of XXXXXXXXXX for the IFN-beta-1a active ingredient when the bulk substance is stored at XXXXXXXXXX or below. XXXXXXXXXX.
Although there is a XXXXXXXXXX stability testing program ongoing, there is only XXXXXXXXXX full scale production lot (XXXXXXXXXX) that has completed the XXXXXXXXXX testing. The XXXXXXXXXX, includes only up to XXXXXXXXXX of stability data. There is real time stability testing for up to XXXXXXXXXX for batches XXXXXXXXXX, which are not full scale production lots. There is also stability data for XXXXXXXXXX qualification lots XXXXXXXXXX submitted; supporting up to XXXXXXXXXX of stability testing. Since there is only stability data for up to XXXXXXXXXX of storage for XXXXXXXXXX full scale batches of product substance, only a XXXXXXXXXX retest period can be granted at this time.

DRUG PRODUCT STABILITY

General

Primary Stability Data

The stability section provided in the BLA contains data for up to XXXXXXXXXX real-time data (2-8°C) for XXXXXXXXXX batches of Rebif 22mcg and XXXXXXXXXX batch of Rebif 44mcg, and up to XXXXXXXXXX accelerated data (XXXXXXXXXX) for XXXXXXXXXX batches of Rebif 22mcg (6MIU) and XXXXXXXXXX batch of Rebif 44mcg (12 MIU). There is also XXXXXXXXXX real time stability data on XXXXXXXXXX batch of Rebif 44mcg and XXXXXXXXXX batches of Rebif 22mcg and XXXXXXXXXX accelerated stability data on XXXXXXXXXX batch of Rebif 22mcg and XXXXXXXXXX batches of Rebif 44mcg. All batches tested are manufactured by XXXXXXXXXX, and are representative of the product intended for marketing. The batches used for the 22mcg filled syringes are: XXXXXXXXXX. Batches used for the 44mcg pre-filled -syringes are: XXXXXXXXXX.

Supportive Stability Data

Supportive stability data for up to XXXXXXXXXX at 2-8°C, was obtained on one batch each, of Rebif XXXXXXXXXX in XXXXXXXXXX and Rebif 44mcg in XXXXXXXXXX, in glass pre-filled syringes. The corresponding batches; XXXXXXXXXX were made at XXXXXXXXXX, not at the production site. The formulation of these batches correspond to that of the product intended for the treatment of XXXXXXXXXX, which is not identical to the formulation used for Multiple Sclerosis. Stability storage for up to XXXXXXXXXX are included for the two batches.

The parameters for Real time and accelerated testing include the following: Appearance/Clarity, Color, pH, Antiviral activity, Assay, XXXXXXXXXX and XXXXXXXXXX substances, Sterility and pyrogens.

Storage Conditions and Parameters Tested

Real Time Testing

Up to XXXXXXXXXX real time stability data (2-8°C) for XXXXXXXXXX Rebif 22mcg and XXXXXXXXXX 44mcg batch and XXXXXXXXXX real time data for XXXXXXXXXX Rebif 22 mcg and XXXXXXXXXX 44mcg batches have been tested. The testing parameters include the following:

1. Identification of container
2. Clarity/opalescence Appearance of solution
3. Color of solution
4. pH
5. Osmolarity
6. XXXXXXXXXX
7. XXXXXXXXXX
8. Assay
9. XXXXXXXXXX
10. XXXXXXXXXX
11. Sterility
12. Bacterial endotoxins

The storage/testing times will be XXXXXXXXXX.

Accelerated Stability Testing

Accelerated stability studies will be performed at XXXXXXXXXX for the following storage times: XXXXXXXXXX. Currently there are stability data for up to XXXXXXXXXX for XXXXXXXXXX batches of 22mcg and XXXXXXXXXX batch of Rebif 44mcg. Also included is up to XXXXXXXXXX stability data for XXXXXXXXXX batches of Rebif 44mcg and XXXXXXXXXX batch of Rebif 22mcg. There is XXXXXXXXXX accelerated stability data for the XXXXXXXXXX supportive batches of Rebif XXXXXXXXXX and Rebif 22mcg/XXXXXXXXXX. The samples are tested for the following:

1. Identification of container
2. Clarity/opalescence
3. Appearance of solution
4. Color of solution

5. pH
6. Osmolarity
7. **XXXXXXXXXX**
8. XXXXXXXXXX
9. Activity Assay
10. XXXXXXXXXX
11. XXXXXXXXXX.

RESULTS

Real Time (Long Term) Stability of Rebif

Real time stability results on XXXXXXXXXX batches of Rebif, XXXXXXXXXX of 22mcg and XXXXXXXXXX of 44mcg are reported. XXXXXXXXXX real time data is available for XXXXXXXXXX Rebif 22mcg and XXXXXXXXXX 44mcg batches, and XXXXXXXXXX real time data are available for XXXXXXXXXX Rebif 22mcg and XXXXXXXXXX Rebif 44mcg batches. The testing results from XXXXXXXXXX batch of Rebif 22mcg and 44mcg are shown below.

Long Term Stability of REBIF 22mcg in pre-filled syringes manufactured by XXXXXXXXXX and stored at 2-8°C (Batch XXXXXXXXXX).

Test	Specification	Storage time (months) at 2-8°C XXXXXXXXXX
Identification of container	**XXXXXXXXXX**	**XXXXXXXXXX**
Appearance of Solution	**XXXXXXXXXX**	**XXXXXXXXXX**
Clarity/opalescence	**XXXXXXXXXX**	**XXXXXXXXXX**
Color of solution	**XXXXXXXXXX**	**XXXXXXXXXX**
PH	**XXXXXXXXXX**	**XXXXXXXXXX**
Osmolarity	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
Assay	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**

Long Term Stability of Rebif 44mcg in pre-filled syringes manufactured by XXXXXXXXXX And stored at 2-8° C (Batch XXXXXXXXXX).

Test	Specification	Storage time (months) at 2-8° C XXXXXXXXXX
Identification of container	**XXXXXXXXXX**	**XXXXXXXXXX**
Appearance of Solution	**XXXXXXXXXX**	**XXXXXXXXXX**
Clarity/opalescence	**XXXXXXXXXX**	**XXXXXXXXXX**
Color of solution	**XXXXXXXXXX**	**XXXXXXXXXX**
PH	**XXXXXXXXXX**	**XXXXXXXXXX**
Osmolarity	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**

Assay	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**

NMT= not more than NLT= not less than P= Passed

Accelerated stability studies:
XXXXXXXXXX batches of Rebif 22mcg and XXXXXXXXXX batches of Rebif 44mcg in pre-filled syringes have been tested at XXXXXXXXXX as stated above. Results from up to XXXXXXXXXX of XXXXXXXXXX batch of Rebif 22mcg and XXXXXXXXXX batch Rebif 44mcg are shown below.

Accelerated Stability of Rebif 22mcg solution for injection in glass pre-filled syringes Made by XXXXXXXXXX and stored at XXXXXXXXX (Batch XXXXXXXXXX).

Test	**Specification**	**Storage time (months) at XXX XXXXXXXXX**
Identification Of container	**XXXXXXXXXX**	**XXXXXXXXX**
Appearance of Solution	**XXXXXXXXXX**	**XXXXXXXXX**
Clarity/opalescence	**XXXXXXXXXX**	**XXXXXXXXX**
Color of solution	**XXXXXXXXXX**	**XXXXXXXXX**
PH	**XXXXXXXXXX**	**XXXXXXXXX**
Osmolarity	**XXXXXXXXXX**	**XXXXXXXXX**
XXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXX**
XXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXX**
Assay	**XXXXXXXXXX**	**XXXXXXXXX**
XXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXX**
XXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXX**

Accelerated Stability of Rebif 44mcg solution for injection in glass pre-filled Syringes made by XXXXXXXXXX and stored at XXXXXXXXXX (Batch XXXXXXXXXX).

Test	Specification	Storage time (months) at XXXXXXXXXX XXXXXXXXXX
Identification Of container	**XXXXXXXXXX**	**XXXXXXXXXX**
Appearance of Solution	**XXXXXXXXXX**	**XXXXXXXXXX**
Clarity/opalescence	**XXXXXXXXXX**	**XXXXXXXXXX**
Color of solution	**XXXXXXXXXX**	**XXXXXXXXXX**
PH	**XXXXXXXXXX**	**XXXXXXXXXX**
Osmolarity	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
Assay	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**
XXXXXXXXXX	**XXXXXXXXXX**	**XXXXXXXXXX**

CONCLUSION:

Primary stability data: The XXXXXXXXXX data currently available on XXXXXXXXXX batches Rebif 22mcg and XXXXXXXXXX batch Rebif 44mcg and XXXXXXXXXX data on XXXXXXXXXX batch Rebif 22mcg and XXXXXXXXXX batches Rebif 44mcg stored at normal conditions (2-8°C), have shown a good product stability profile. There is a trend of Rebif 22mcg and 44mcg pre-filled syringes to form XXXXXXXXXX and a small amount of XXXXXXXXXX of IFNβ-1a XXXXXXXXXX. The other parameters tested do not currently show any trend. No loss of biological activity has been recorded. All batches of Rebif are tested in prefilled syringes in the final container.

Supportive Stability Data: The results from one batch of Rebif XXXXXXXXXX mcg and 44mcg (XXXXXXXXXX) for both long term and accelerated testing confirm the stability results obtained from the primary stability data.

Expiration Dating and storage: Serono claims a 24 month shelf life for Rebif pre-filled syringes when stored at 2-8°C. Currently there is only data of up to XXXXXXXXXX for XXXXXXXXXX lots of Rebif 22mcg and XXXXXXXXXX lot of Rebif 44mcg available. Therefore, the agency can only grant a XXXXXXXXXX self life at this time for both Rebif 22mcg and 44mcg pre-filled syringes. The supportive stability data available is for up to XXXXXXXXXX, but the batches tested are not manufactured at the production site and formulation is different than that used for the final formulation of the marketed product.

Comments to Sponsor

Shipping Validation:

1. Please provide supporting data validating that the bulk drug substance is maintained at the appropriate temperature during shipment from the production site to the final formulation site. This data should include an SOP describing test methods used and how data is recorded.
2. Please provide data to validate shipping conditions of the final formulated drug product to the distribution site. Validation should include SOPs describing test methods and how data is recorded.

Drug Substance:

1. Please provide any additional real time stability data for production batch XXXXXXXXXX beyond the XXXXXXXXXX test period currently available.
2. Please submit any additional real time stability data for qualification lots: XXXXXXXXXX beyond the XXXXXXXXXX test period.

Drug Product:

1. Please submit real time and accelerated stability data for the XXXXXXXXXX batches of Rebif (XXXXXXXXXX of Rebif 22mcg and XXXXXXXXXX of Rebif 44mcg) beyond the XXXXXXXXXX test periods currently available.